SINGLE CHANNEL REFORMATTER

Field of the Invention

The present invention relates to an article for handling small volumes of liquid. More particularly, the present invention relates to an article capable of transferring liquid, on a well-to-well basis, from a source container having a first format or configuration (*e.g.*, a 96-well micro-titer plate, a vial, *etc.*) to a destination container having a second format (*e.g.*, a 1536-well micro-titer plate).

Background of the Invention

Advances in the field of combinatorial chemistry, high throughput screening and genomics research have pushed liquid handling capabilities of conventional devices and instrumentation to the limit with regard to high-speed handling of micro-volumes of liquid (*i.e.*, from 0 to about 2 microliters). Specifically, many of the techniques used in such fields require aspirating liquid from and dispensing liquid into micro-titer plates or other containers configured to retain very small quantities of liquid.

Progress in the aforementioned fields is generating a need to miniaturize assay format from, for example, the common 96-well micro-titer plate (6.5 mm well diameter) to 384-well plates (3.5 mm square wells) and to state-of-the-art 1536-well plates (1.3 mm well diameter). With these and other assay formats in use, situations arise wherein liquid must be transferred between plates having different formats. The usual application is transferring liquid from a relatively lower density format, such as a 96-well plate, to a relatively higher density format, such as 384- or 1536-well plates. This transfer of liquid between plates having different formats is referred to as "reformatting."

Tools are available for *en masse* reformatting. *En masse* reformatting is when the contents of *groups* of wells or even *all* the wells of a plate having a first format are transferred, in a single operation, to the wells of a plate having a second format. The devices for doing such *en masse* reformatting typically use a plurality of syringes (*e.g.*, 8 syringes or 96 syringes are common) that aspirate the contents of the wells of, for example, a 96-well plate, and dispense the aspirated liquid into the wells of higher density plates.

Of late, there has been interest in reformatting on a *well-by-well* basis. In other words, rather than *en masse* reformatting, a need has arisen to transfer the contents of a particular well in a source plate to a particular well in a destination plate. The prior art offers little in the way of technology for this application.

One option, at least in theory, for well-to-well reformatting is to reformat manually using a pipette. In practice, this is impractical if not impossible. Aside from an inability to achieve a sufficient throughput rate for commercial scale operation, it is probably beyond the capabilities of a human to accurately or repeatedly pipette liquid into the 1.3 mm wells of a 1536 well plate.

Another solution in the prior art for well-to-well reformatting is to use a single pipette head that is attached to an x-y-z-positioner, such as is described in U.S. Pat. No. 4,979,093 ("the '093 patent") assigned to Cavro Scientific Instruments. The "single channel" (*i.e.*, one pipette) arrangement for dispensing that is described in the '093 patent is depicted herein in FIG. 1.

Arrangement **100** depicted in FIG. 1 includes two variable length arms **102** and **104** that are connected to hinge **106** and to respective pivots **108** and **110**. Stepper motors (not shown) that are disposed within pivots **108** and **110** change the length of arms **102** and **104** via friction drive wheels and pinch rollers (not shown). Storage reels (not shown) that are disposed in pivots **108** and **110** accommodate changes in the length of arms **102** and **104**. Changing the length of the arms causes movement in the x-y plane.

Receiver **107**, which is connected to arms **102** and **104**, engages pipette **124**. Pipette **124** is operatively connected to z-motion controller **116** via an "actuator/flow tube" (not shown) that is disposed within guide tube **114**. The actuator/flow tube slides within actuation guide **114** when actuated by z-motion controller **116**. Such sliding movement of the actuator/flow tube causes pipette **124** to move along the z-axis (*i.e.*, vertically).

The actuator/flow tube is also connected to fluid dispenser **118**. Fluid dispenser **118** is operative to cause pressure changes within the actuator/flow tube. Negative relative pressure enables pipette **124** to aspirate fluid, such as from wells **128** in source plate **126**. Conversely, positive relative pressure enables pipette **124** to dispense aspirated fluid, such as into wells **132** in destination plate **130**.

Source plate **126** and destination plate **130** are registered in a known position on a stationary platform (not shown). The x-y-z coordinates of any well **128** in source plate **126** and the x-y-z coordinates any well **132** in destination plate **130** can therefore be determined. To aspirate from well **128A** in source plate **126** and then dispense the aspirated liquid into well **132-**

19 in destination plate **130**, computer **120** transmits the corresponding x-y-z coordinates of the source and destination wells to controller **122**. Controller **122** converts the coordinates into motor control information that drives the motors (not shown) that control the arms **102** and **104** and the z-motion controller **116**.

There are a number of shortcomings or problems with the apparatus described in the '093 patent. In particular, the positioning operation is relatively slow and disadvantageously exhibits characteristically low positioning and dispensing accuracy since all major liquid dispensing functions are operated on a moving, cantilevered liquid carrier (*i.e.*, the pipette).

Moreover, this device introduces inefficiency (*i.e.*, time delays) as a result of the manner in which a series of transfers are effected. That is, liquid transfers are typically sequenced without regard to the relative positions, in successive cycles, of the source and destination wells.

Furthermore, it will be appreciated that the syringe of a reformatter must be washed between dispenses to avoid possible cross contamination. Prior art reformatters and liquid dispensers in general have very inefficient wash cycles. In particular, in such devices, the working pipette is typically transported to and from a wash station, increasing the operating-washing-operating cycle time. Moreover, wash operations require internal and external washing of the working pipette, so that the washing operation creates a substantial waste problem in view of the number of washes involved and the relatively wasteful manner in which wash solution is used.

A need therefore exists for an improved single channel reformatter.

Summary of the Invention

The present invention provides, in some embodiments, a single channel reformatter that avoids the drawbacks of the prior art. In particular, the present reformatter is fast and has very high positioning and dispensing accuracy. Such speed and accuracy is achieved, in part, by disposing the source and destination plates on a x-y stage. Rapid and precise motion is more readily obtained by moving the plates on a x-y stage than by moving a pipette at the end of a cantilevered arrangement as in the prior art.

Moreover, in some embodiments of the present invention, the liquid transfer vehicle (*i.e.*, pipette, syringe, *etc.*) is limited to z-axis motion and, in fact, is mechanically de-coupled from the x-y stage. A repeatable, accurate dispensing operation is more readily obtained with a syringe,

etc., that is stationary in the x-y plane than with one that is moving in three dimensions at the end of a cantilevered arrangement as in the prior art.

In a further embodiment, the present invention provides an efficient wash system that advantageously operates between successive plate-to-plate transfer operations (hereinafter "normal liquid transfer operations" or "working cycle"). Since, in accordance with the present teachings, the liquid transfer vehicle does not travel in the x-y plane during the working cycle, it can be, and advantageously is, integrated directly into such a wash system. In such an integrated system, no time is lost, as with prior art dispensers, in moving the liquid transfer vehicle to a wash station and back again for the subsequent working cycle.

In some embodiments, the wash system comprises two syringes—a wash syringe and a waste syringe—in addition to the liquid transfer vehicle. In such embodiments, the liquid transfer vehicle is advantageously configured as a syringe (hereinafter the "working syringe"). The three syringes are in fluidic communication with one another and with supply and waste reservoirs. Further, the three syringes and their plungers cooperate mechanically with a single drive mechanism such that a "stroke" of the drive aspirates (dispenses) the working syringe and the waste syringe while, at the same time, the wash syringe is dispensed (aspirated). Moreover, in some embodiments, the drive element that actuates the plungers during the wash cycle is used during normal liquid transfer operations.

The present invention also provides a method for controlling the reformatting operation. The method advantageously comprises: (1) specifying well-to-well links, (2) determining a preferred execution order for executing the specified links thereby enhancing reformatting efficiency, and (3) executing the specified links in the preferred order. In some embodiments, the preferred execution order sequences links based on the relative locations of "destination wells" (*i.e.*, wells that receive liquid from the source plate) in successive cycles.

Brief Description of the Drawings

FIG. 1 depicts an arrangement for single channel reformatting in the prior art.

FIG. 2 depicts a conceptual or figurative view of an illustrative embodiment of a single channel reformatter in accordance with the present invention.

FIG. 3 depicts a specific embodiment of the reformatter depicted in FIG. 2.

FIG. 4 depicts the x-y positioner of the single channel reformatter of FIG. 3.

FIG. 5 depicts a conceptual or figurative view of an illustrative embodiment of a z-positioner for use in conjunction with the single channel reformatters of FIGS. 2 and 3.

FIG. 6 depicts the z-positioner of FIG. 5 as well as a syringe drive for causing aspirating and dispensing action in the working syringe.

FIG. 7 depicts an illustrative embodiment of a wash system in accordance with the present teachings.

FIGS. 8A-8C depict the position of the plunger and the direction of its movement within each of the three syringes comprising the illustrative wash system of FIG. 7.

FIG. 9 depicts a method for operating the present single channel reformatter.

FIG. 10 depicts processing and control electronics for controlling the various positioners and drives used in conjunction with the present single channel reformatter.

FIG. 11 depicts an illustrative graphical user interface for use in conjunction with the present single channel reformatter.

FIGS. 12 and 13 depict an illustrative methodology for tracking specified links using the graphical user interface of FIG. 11.

FIG. 14 depicts an illustrative data structure for organizing link data.

Detailed Description

The illustrative embodiments of the present invention that are described herein and depicted in the accompanying drawings are directed to a single channel reformatter. This *Detailed Description* begins with a description of the functional elements of such a single channel reformatter. This approach is useful for pedagogical purposes in that it provides increased clarity of presentation and generality of description.

The description of functional elements is followed by a description of several specific structural embodiments. It should be understood that the specific structural embodiments are provided by way of illustration, not limitation. Moreover, the principles, apparatuses and methods described in this *Specification* have applicability beyond the illustrated reformatting application. For example, a wash system and x-y-z positioning system disclosed herein may suitably be used to improve the operation of a variety of liquid-handling apparatuses. And, with modifications that are within the capabilities of those skilled in the art, the principles, apparatus and methods

described herein are readily extended to applications other than liquid handling. Such variations and modifications are within the contemplated scope of the present invention.

FIG. 2 depicts an illustrative single channel reformatter ("SCR") **200** in accordance with the present teachings. Illustrative SCR **200** includes x-y positioner **201**, z-positioner **206**, optional integrated wash station **208**, liquid transfer vehicle **210**, fluid control device **212**, and processing and control electronics **214**, interrelated as shown.

Z-positioner **206** is operable to move liquid transfer vehicle **210** upwardly and downwardly (*i.e.*, along the z-axis) as directed by processing and control electronics **214**. The term "**liquid transfer vehicle**," as used herein, means syringe, pipette, capillary tube, nozzle or like element suitable for delivering (possibly in conjunction with an element for causing aspirating or dispensing flow) a desired amount of liquid at a desired location. In the illustrated embodiments, the liquid transfer vehicle is a syringe, and will henceforth be referred to as "**working syringe 210**." Working syringe **210** is moved downwardly, for example, in preparation for dispensing liquid into a container positioned beneath it, and moved upwardly to allow that container to be moved away to allow another container to take its place.

The x-y positioner **201** comprises x-y drive **204** that is operable, when actuated, to precisely and accurately move x-y stage **202** in the x-y plane. In the illustrated embodiment, x-y stage **202** comprises a surface that is suitable for receiving source container **250** from which liquid is aspirated. Stage **202** is also suitable for receiving destination container **260** into which the aspirated liquid is dispensed. In the embodiments described herein, source container **250** is a micro-titer plate having a plurality of wells **152** and destination container **260** is a micro-titer plate having a plurality of wells **162**. It should be understood, however, that other types of containers may suitably be used in conjunction with the present invention.

With source plate **250** and destination plate **260** disposed on x-y stage **202**, x-y positioner **201** is operable to: (1) position any of the wells **152** of plate **250** under working syringe **210** so that liquid contained in such wells can be aspirated into working syringe **210**, and (2) position any of the wells **162** of plate **260** under working syringe **210** so that liquid that has been aspirated into syringe **210** can be dispensed into such wells.

To perform well-to-well liquid transfer operations, the spatial location of each well must be known. To that end, x-y stage **202** has physical adaptations (not shown in FIG. 2) for receiving plates **250** and **260** at predetermined locations. Given a particular plate format (*e.g.*, 96-well, 384-well, *etc.*) and the location of the plate at either the source plate position or at the

destination plate position on x-y stage **202**, the spatial location of each well, in terms of x, y and z coordinates, is readily determined.

When appropriately positioned in a specified well **152** in source plate **250** by the action of positioners **201** and **206**, a suction (*i.e.*, negative relative pressure) is developed in working syringe **210** to aspirate a desired amount of liquid from that well. After aspirating the liquid, working syringe **210** is moved vertically (*i.e.*, along the z-axis) out of the well. The x-y stage **202** is then advanced to move a specified well **162** in destination plate **260** in to position beneath working syringe **210**. Working syringe **210** then moves downwardly under the action of z-positioner **206**. Once in position in well **162**, the fluid within working syringe **210** is dispensed.

The aspirating and dispensing ("fluid control") functions of syringe **210** are accomplished via fluid control device **212**. The term "**fluid control device**," as used herein, means pump, vacuum pump, ejector, or other arrangement capable for generating aspirating or dispensing flow through the liquid transfer vehicle (*e.g.*, working syringe **210**). Since, in the illustrated embodiments, a syringe (as opposed to a pipette, *etc.*) is used as the liquid transfer vehicle, the fluid control functions are advantageously implemented by simply drawing the plunger away from the bottom of body of the syringe, or pushing it towards the bottom of the body of the syringe. Thus, the meaning of the term "**fluid control device**" also encompasses a mechanism suitable for moving the plunger in the aforementioned fashion. In recognition of the fact that the illustrated embodiments depict a syringe as the liquid transfer vehicle, the fluid flow controller will henceforth be referred to as "**syringe drive 212**." The term "**syringe drive**," as used herein, thus refers to a mechanism suitable for moving the plunger in the aforementioned fashion. Those skilled in the art will recognize that many mechanisms are suitable for such service. By way of illustration, not limitation, the embodiments depicted herein utilize a linear drive mechanism for this purpose. As used herein, the term "**linear drive mechanism**" refers to any mechanism capable of moving an object in linear motion.

Z-positioner **206**, x-y positioner **201** and syringe drive **212** are actuated by processing and control electronics **214**. The processing and control electronics, which is capable of performing the functions described below, is suitably implemented using either shared or dedicated hardware, including, without limitation, hardware capable of executing software.

Provided with "link data" specified by a user (*e.g.*, transfer liquid from the well located in the source plate at row 2, column 7 to destination well (15,20), *etc.*), the spatial coordinates of the wells involved in the transfer, and several other control parameters described later, processing and control electronics **214** is operable to:

(1) actuate x-y positioner **201** to move a well **152** into position under syringe **210**;

(2) actuate z-positioner **206** to lower working syringe **210** into well **152**;

(3) actuate syringe drive **212** to aspirate liquid from well **152** into working syringe **210**;

(4) actuate z-positioner **206** to raise working syringe **210** out of well **152**;

(5) actuate x-y positioner **201** to move a well **162** into position under syringe **210**;

(6) actuate z-positioner **206** to lower working syringe **210** into well **162**;

(7) actuate syringe drive **212** to dispense liquid from syringe **210** into well **162**; and

(8) actuate z-positioner **206** to raise working syringe **210** out of well **162**.

To the extent that different fluids are being handled in subsequent liquid handling cycles, cross contamination will occur unless working syringe **210** is washed. To that end, working syringe **210** is advantageously washed via wash system **208** after an aspirating/dispensing cycle. Wash station **208** advantageously washes the inside and the outside of working syringe **210** to substantially reduce the risk of cross contamination. Processing and control electronics **214** controls the wash operation.

As already discussed, working syringe **210** is advantageously not moved in the x-y plane. As a consequence, in some embodiments of the present invention, working syringe **210** is incorporated directly into wash system **208**. A first benefit of such incorporation is that time is saved by not having to transfer working syringe **210** to a wash station and back again. A second benefit of such incorporation is that, when wash station **208** is appropriately configured, syringe drive **212** advantageously provides both the fluid control function during normal liquid transfer operations and also drives the wash station operations. An illustrative embodiment of wash system **208** and its workings is described later in this *Specification*.

This *Specification* continues with a description of FIGS. 3-14, which provide illustrative structural details for the functional description provided above. Structures depicted in these Figures will be cross-referenced, as appropriate, to the more functional representations provided in FIG. 2.

FIG. 3 depicts an embodiment of SCR **200**. The various positioning, dispensing and wash structures that comprise SCR **200** are advantageously anchored by a frame comprising base plate **320**, back plate **322**, left side **324** and right side **326**, interrelated as shown in FIG. 3. Base plate **320** provides support for the x-y positioner **201** and back plate **322** provides support for z-positioner **206** and wash system **208**. Left side **324** and right side **326** support back plate **322**.

The x-y positioner **201**, which, for the sake of clarity, is depicted sans z-positioner **206** and wash station **208** in FIG. 4, comprises an x-positioner "piggybacked" on a y-positioner. The y-positioner includes y-plate or y-stage **436** and two linear bearings **432** and **434** that are disposed on respective bearing spacers **428** and **430**. The bearing spacers **428** and **430**, which are attached to base plate **320** near the edges of the long sides thereof, raise linear bearings **432** and **434** (and y-plate **436**) above base plate **320** to allow room for underlying y-drive **438** and the x-drive (not shown).

Slides **442** are mounted on the underside of y-plate **436** so that they engage linear bearings **432** and **434**. Slides **442** promote low-friction movement of y-plate **436** over linear bearings **432** and **434**. Y-drive **438** controls the movement of y-plate **436** along the linear bearings. In the illustrated embodiment, y-drive **438** is configured as a linear drive mechanism. The particular linear drive mechanism depicted comprises y-stepper motor **440** that drives a ball screw assembly (not shown in FIG. 4) in well-known fashion. Y-stepper motor **440** is attached to base plate **320** and the ball screw assembly is engaged to the underside of y-plate **436**. Y-plate **436** is driven along linear bearings **432** and **434** along the y-axis as y-stepper motor **440** turns, as dictated by processing and control electronics **214** (FIG. 2).

Linear bearings **432**, *etc.*, slides **442**, *etc.*, and the ball screw assembly are available from NSK Corporation of Schaumberg, Illinois. Machined parts, such as bearing spacers **428**, *etc.*, can be fabricated to specification by Manheim Corporation of Collegeville, Pennsylvania. Stepper motor **440** is available from Applied Motion Products of Watsonville, California.

The x-positioner, which is piggybacked on the y-positioner, includes x-plate or x-stage **448** and two linear bearings **444** and **446** that are disposed near the edges of the long sides of y-plate **436**. Slides **450** are mounted on the underside of x-plate **448** so that they engage linear bearings **444** and **446** to facilitate low-friction movement of x-plate **448**. The x-drive (not depicted) controls the movement of x-plate **448** along linear bearings **444** and **446**. In some embodiments, the x-drive is configured as a linear drive mechanism (not shown), such as the combination of a stepper motor driving a ball screw assembly.

As previously described, x-plate **448** has physical adaptations for receiving source containers **250** and destination containers **260** at predetermined locations. In the illustrated embodiment, the containers **250**, **260** are micro-titer plates, and the physical adaptations are guides **452** and **454** that define source plate receiver **456** and guides **458** and **460** that define destination plate receiver **462**, both appropriately sized and shaped for receiving micro-titer plates. In other embodiments (not shown), the guides are movable such that the size of the

receiver can be changed to accommodate containers other than plates. In still other embodiments, the guides are replaced with various clamping devices as may be appropriate for receiving certain types of liquid containers.

Illustrative z-positioner **206** is depicted, sans x-y positioner **201**, in FIGS. 5 and 6. Z-positioner **206** is depicted, in the illustrative embodiment, as a linear drive mechanism. The particular linear drive mechanism shown comprises z-stepper motor **570** driving ball screw assembly **572**.

As depicted in FIG. 5, working syringe **210** is secured to frame **578**, which, in turn, is operatively engaged to ball screw assembly **572**. Specifically, in the illustrated embodiment, screw or shaft **574** receives frame **578** in sliding engagement above ball nut **576**. Frame **578** is also slidingly engaged (via slides **580** that depend from frame **578**) to linear bearing **582**, which is itself attached to back plate **322**. As a consequence, frame **578** slides over linear bearing **582** along direction vector **581** (*i.e.*, along the z-axis) as urged by ball nut **576** on screw **574** under the action of z-stepper motor **570**.

As previously mentioned, in some embodiments of the present invention, working syringe **210** is integrated into wash system **208**. In those embodiments, it is advantageous to mechanically link wash system **208** to frame **578** so that appropriate elements of wash system **208** move in concert with working syringe **210**. In other words, as a result of such a connection, there is no *relative* motion between wash system **208** and working syringe **210**. Such a mechanical link is depicted figuratively in FIG. 5.

FIG. 6 depicts z-positioner **206** and syringe drive **684** disposed on back plate **322**. Syringe drive **684** provides fluid control functions (*i.e.*, aspirating and dispensing) for working syringe **210**. Syringe drive **684** can be, for example, a linear drive mechanism like the x-, y- and z-drives previously described. In the illustrated embodiment, syringe drive **684** comprises s-stepper motor **686** and ball screw assembly **688**.

Syringe drive **684** operatively engages plunger **211** of working syringe **210**. In particular, in the illustrated embodiment, coupling member **694** engages plunger **211** of working syringe **210** while screw **690** receives coupling member **694** in sliding engagement above ball nut **692**. As a result of such engagement, coupling member **694** and plunger **211** are moved along direction vector **696** (*i.e.*, along the z-axis) responsive to movements of ball nut **692** on screw **690** under the action of s-stepper motor **686**. Coupling member **694**, and any other structural members (*e.g.*, plates, *etc.*), may suitably be formed from anodized aluminum.

As previously indicated, in some embodiments, syringe drive **684** is advantageously used to drive wash systems operations, as well as normal liquid transfer operations. In such embodiments, syringe drive **684** is advantageously piggybacked on z-positioner **206** such that syringe drive **684** moves with syringe **210** on z-axis movements. This arrangement is illustrated in FIG. 6 (*see* attachment of s-stepper motor **686** to frame **578**).

It should be understood that, in the illustrated embodiment, syringe drive **684** does *NOT* change the position of working syringe **210**. Rather, syringe drive **684** changes the position of plunger **211**. Syringe drive **684** therefore causes a relative motion ***RM*** between the body of the syringe **210** and plunger **211**. Upward movement of plunger **211** thus generates a suction flow that causes any liquid in contact with the tip of working syringe **210** to be aspirated therein. Downward movement of plunger **211** generates a positive pressure that forces any liquid that is within working syringe **210** to be dispensed therefrom. And, as previously noted, in embodiments in which syringe drive **684** is piggybacked on z-positioner **206** and therefore moves along with working syringe **210**, the z-positioner is *not* operative to cause a relative motion between plunger **211** and working syringe **210**. In other words, z-positioner **206** does not generate any aspirating or dispensing action in working syringe **210**.

In embodiments in which working syringe **210** is integrated into wash system **208**, any movement of plunger **211** relative to the body of working syringe **210** during liquid transfer operations will affect flow conditions in wash system components. Those effects will be described later in this *Specification.*

FIG. 7 depicts an illustrative embodiment of wash system **208** in accordance with the present teachings. For clarity of illustration, syringe drive **684** is not shown in FIG. 7. For reference, syringe drive **684** engages coupling member **694** (as illustrated in FIG. 6). For further perspective, *see* FIG. 3, wherein wash system **208** is depicted in conjunction with other elements of illustrative SCR **200**.

Illustrative wash system **208** includes two syringes in addition to working syringe **210**. The additional syringes include wash syringe **702** having plunger **703** and waste syringe **704** having plunger **705**. Wash syringe **702** supplies cleaning fluid to working syringe **210**, while waste syringe **704** provides a suction flow that removes contaminated cleaning fluid from well **707** in wash/waste station **706** after it is has been used to wash working syringe **210**.

Illustrative wash system **208** also includes supply reservoir **708** and waste reservoir **710**. Supply reservoir **708** supplies cleaning fluid to wash syringe **702**, and waste reservoir **710**

receives the contaminated cleaning fluid that waste syringe **704** has aspirated from well **707**. The supply reservoir and the waste reservoir may suitably be realized as standard flasks.

Various conduits place the various syringes in fluid communication with supply reservoir **708**, waste reservoir **710** and wash/waste station **706**. Wash/waste station **706** is made out of a material that is selected for chemical compatibility with the cleaning fluid and various reagents. Polyethylene has been found to be an acceptable material for most applications.

In accordance with the present teachings, plunger **211** of working syringe **210** and plunger **705** of waste syringe **704** cooperate mechanically with coupling member **694** such that those two syringes aspirate together and dispense together. On the other hand, wash syringe **702** and its plunger **703** are configured such that wash syringe **702** aspirates while the waste and working syringe dispense, and wash syringe **702** dispenses while the waste and working syringe aspirate. In accordance with some embodiments of the present invention, plungers **211**, **705** and **703** are all moved by the same actuating device (*i.e.*, syringe drive **684**) at the same time.

The operation of wash station **208** is now described with reference to the flow of cleaning fluid through the wash system as a function of syringe drive movements, as depicted in FIGS. 7 and 8A-8C.

FIG. 8A depicts the "state" of the three syringes, and their associated plungers, at the beginning of the previous operation (*i.e.*, before the wash cycle) wherein working syringe **210** is about to dispense reagent into destination plate **260**. As depicted in FIG. 8A, as plunger **211** is moved downwardly (via the action of syringe drive **684**) so that working syringe **210** can dispense reagent into a well in a destination plate, plunger **703** is moved upwardly (via the same movement of syringe drive **684**).

As plunger **703** moves upwardly creating a suction flow, check valve **714** opens and check valve **718** closes due to the one-way nature of such check valves. With check valve **714** open, cleaning fluid is aspirated from supply reservoir **708** through reservoir supply conduit **712** and through wash syringe conduit **716** into wash syringe **702**. The check valves, which should have a low cracking pressure (1.5 psi has been found to be acceptable), are available from Upchurch Scientific of Oakharbor, WA. All conduit used in wash system **208** should be selected for chemical compatibility with the chemicals being used. Teflon is suitable for many applications.

As plunger **211** of working syringe **210** is forced downwardly, plunger **705** of waste syringe **704** is also forced downwardly. As this occurs, any used cleaner that had been drawn into

waste syringe **704** (*see* description accompanying FIG. 8B) is dispensed, closing check valve **724** and opening check valve **726**. With check valve **726** open, used cleaning fluid is forced through waste reservoir conduit **728** into waste reservoir **710**.

Note the efficiency provided by (1) the integration of working syringe **210** into wash station **208**; and (2) driving both working syringe **210** and wash system **208** with syringe drive **684**. In particular, wash system **208** is advantageously readying for the next wash cycle *during* normal liquid transfer operations and is actuated by the *same* drive that is dispensing working syringe **210** during normal liquid transfer operations.

FIGS. 7 and 8B depict the state of the three syringes and their plungers after reagent has been dispensed from working syringe **210** into destination plate **260**. In FIG. 7, wash/waste station **706** has been positioned under working syringe **210** via x-y positioner **201**, and z-positioner **206** has dropped working syringe **210** into working syringe supply conduit **720**. Working syringe **210** is therefore ready to aspirate cleaning fluid.

As plunger **703** is moved into wash syringe **702** (via the action of syringe drive **684**), cleaning fluid is dispensed therefrom. Due to the flow of cleaning fluid out of wash syringe **702** and through wash syringe conduit **716**, check valve **714** closes and check valve **718** opens. With check valve **718** open, cleaning fluid flows into working syringe supply conduit **720**. As plunger **703** moves into wash syringe **702**, plunger **211** moves upwardly out of working syringe **210**. This upward movement creates a suction flow that aspirates cleaning fluid into working syringe **210**. Also, as a consequence of its position partially within working syringe supply conduit **720**, the exterior of the needle or tip of working syringe **210** is washed with cleaning fluid.

Waste syringe **704** aspirates with working syringe **210**. The upward movement of plunger **705** creates a suction flow that opens check valve **724** and closes check valve **726**. Contaminated cleaning fluid in well **707** is drawn into waste supply return conduit **722**, through check valve **724** and into waste syringe **704**.

FIG. 8C depicts the state of the three syringes and their plungers after cleaning fluid is dispensed from wash syringe **702** and aspirated by working syringe **210**. During the next operation, contaminated cleaning fluid is dispensed from working syringe **210**. In preparation for this operation, z-positioner **206** raises working syringe **210** out of working syringe supply conduit **720**.

As plunger **211** is moved downwardly into working syringe **210** (via the action of syringe drive **684**), contaminated cleaning fluid is dispensed from the working syringe into well **707**.

Moreover, waste syringe **704** dispenses its load of contaminated cleaning fluid (*see* description accompanying FIG. 8B) through check valve **726** and waste reservoir conduit **728** into waste reservoir **710**. At the same time, wash syringe **702** aspirates fresh cleaning fluid in the manner previously described (*see* description accompanying FIG. 8A).

After contaminated cleaning fluid is dispensed from working syringe **210**, the next reformatting cycle is ready to begin. And, as the next reformatting cycle begins with working syringe **210** aspirating liquid from a source well, wash syringe **702** dispenses fresh cleaning fluid to working syringe supply conduit **720** thereby forcing any contaminated cleaning fluid in conduit **720** into well **707**. Meanwhile, waste syringe **704** aspirates the contaminated cleaning fluid from well **707**. As previously noted, integrating working syringe **210** into wash system **208**, and using a single drive to "power" both working syringe **210** and wash system **208** provides an extraordinary level of efficiency to the washing operation, in accordance with the present teachings.

The foregoing specific embodiment is generalized by the following description of wash system **208**. In accordance with the present teachings, wash system **208** includes:

a first conduit (conduits **712** and **720)** that is in fluid communication with a supply of cleaning fluid (supply reservoir **708**) and wash/waste station **706**;

a second conduit (conduits **722** and **728**) that is in fluid communication with wash/waste station **706** and waste reservoir **710**; and

a fluid flow controller (syringe drive **684** in conjunction with the plungers/syringes and conduit **716**) for:

generating a flow of cleaning fluid from supply reservoir **708** to said wash/waste station **706**, and

generating a flow of contaminated cleaning fluid from said wash/waste station **706** to said waste reservoir **710**.

To ensure proper flow of cleaning fluid through wash system **208**, which is a closed system, waste syringe **704** should have a greater capacity than wash syringe **702** and the wash syringe has a greater capacity than working syringe **210**. By way of example, capacities of 590, 250 and 100 microliters for waste syringe **704**, wash syringe **702** and working syringe **210**, respectively, have been found to be suitable for use in wash system **208**. The syringes should be high quality, glass syringes such as Hydra syringes, available from Robbins Scientific Corporation of Sunnyvale, California.

FIG. 9 depicts method **900** for controlling SCR **200**. Method **900** is advantageously implemented via processing and control electronics **214**, an illustrative embodiment of which is depicted in FIG. 10.

In the illustrative embodiment depicted in FIG. 10, processing and control electronics **214** includes processor **1042** running interactive SCR control software **1046**. The SCR control software, including updateable data file **1048**, is stored in memory/computer storage device **1044**.

In accordance with operation **930** of illustrative method **900**, one or more "source-to-destination links" (hereinafter "links" or "link data") that define the reformatting operations are specified. Each such link specifies a well in a source plate from which liquid is to be aspirated, and further specifies a well in a destination plate into which the aspirated liquid is to be dispensed. There are, of course, many ways in which operation **930** can be implemented via interactive software, including a variety of user interface options and, also, a variety of different data structures for organizing the link data for use by the software. FIGS. 11-13 depict an illustrative embodiment of a graphical user interface ("GUI") **1100** by which link data and other operating parameters are specified, and FIG. 14 depicts an illustrative embodiment of an array **1454** of data structures **1456_i** for organizing the link data within interactive software **1046**.

Referring now to FIG. 11, in illustrative GUI **1100**, source plate (*e.g.*, source plate **250** of FIG. 2) is selected via icon **1102**. "Clicking" on icon **1102** allows a user to select any of several format options (*e.g.*, 96-well plate, 384 well plate, 1536 well plate, *etc.*). An alphanumeric description of the selected format appears in selection box **1104**. Moreover, graphical representation **1106** of the selected format advantageously appears in GUI **1100**. Graphical representation **1106** depicts a graphical representation **1108** of the appropriate number of wells for the selected format.

The format of the destination plate (*e.g.*, destination plate **260** of FIG. 2) is selected via icon **1112**. A description of the selected format appears in selection box **1114**. Graphical representation **1116** of the destination plate, including a graphical representation **1118** of the appropriate number of wells for the selected format, advantageously appears in GUI **1100**.

In some embodiments, to specify a source well, a user simply "clicks" on graphical representation **1108** of a well in the source plate. Similarly, to select a corresponding destination well, the user clicks on graphical representation **1118** of that well in the destination plate. The selected wells are advantageously "highlighted," and row-column descriptions **1110** and **1120** that identify the selected wells advantageously accompanies the graphical representations.

In other embodiments, the source and destination wells can be selected by specifying a row number and a column number in respective row-column descriptions **1110** and **1120**. In such embodiments, the graphical representations **1108** and **1118** of the specified wells are advantageously highlighted to provide a pictorial description. In yet additional embodiments, the wells can be specified in both of the above-described ways.

Furthermore, rather than specifying new links in operation **930**, SCR control software **1046** and GUI **1100** advantageously allow a user to recall a previously specified group of links that have been stored in memory **1044**.

In some embodiments, graphical representations **1106** and **1116** of the plates keep track of selected links. In particular, in the embodiment depicted in FIG. 12, the current source well selection, which is located in the first row and second column, is highlighted by first color ***R*** (*e.g.*, red, *etc.*), while previously selected source wells are highlighted in second color ***O*** (*e.g.*, orange, *etc.*).

One or more destination wells may be specified for each source well. The destination wells being selected for the currently selected source well are highlighted in first color ***R*** to depict the correspondence between each destination well and the source well. Destination wells that link to previously selected source wells are highlighted by second color ***O***. *See* FIG. 12. A user continues specifying links using GUI **1100** until all intended links are specified.

Link data for previously selected wells is advantageously accessed through GUI **1100**. For example, in one embodiment, such data is accessed by "clicking" on a previously selected source well. As depicted in FIG. 13, accessing the previously selected source well in row 2, column 1 changes that well's highlighting from second color ***O*** to first color ***R***. All destination wells that receive fluid from the source well are also displayed in first color ***R***.

Returning to method **900** depicted in FIG. 9, in optional operation **932**, syringe control parameters are specified, and in optional operation **934**, wash system parameters are specified. Operations **932** and **934** are considered to be optional because SCR **200** could be operated with fixed values for these parameters. It is, however, advantageous to allow a user to specify such parameters.

In the embodiment depicted in FIG. 11, GUI **1100** is configured to accept syringe control parameters. The syringe control parameters included in GUI **1100** of FIG. 11 include the volume of liquid dispensed from working syringe **210** and dispense position corrections **1124**. In the

illustrated embodiment, syringe dispense volume is specified by inserting a number, which does not have to be an integer, in box **1122**.

Regarding position corrections **1124**, a user can specify the radial position of the tip of working syringe **210** within a well, wherein 0% correction corresponds to the center of the well and 100% correction corresponds to the wall or perimeter of the well. This "horizontal" position correction allows a user to create "touch-off" wherein a liquid droplet that forms at the tip of working syringe **210** contacts the wall of the well. Touch-off overcomes surface tension forces that tend to keep the droplet from disengaging from the syringe. The horizontal touch-off correction is specified by moving slider **1126** along the scale, as appropriate. The specified touch-off correction appears in box **1128**.

The "vertical offset" correction specifies how deeply the syringe is positioned in a well, wherein 0% correction corresponds to the bottom of the well and 100% correction corresponds to the top of the well. This feature is particularly useful if, for example, there is another liquid already in the well, since contamination issues may arise if the syringe contacts that liquid. The vertical offset correction is specified by moving slider **1130** along the scale, as appropriate. The specified vertical offset correction appears in box **1132**.

GUI **1100** of FIG. 11 is also configured to accept a *wash system parameter*. In particular, the user may specify the number of wash cycles that wash system **208** performs between reformatting cycles. Wash cycles are specified via icon **1134**. The selected number of cycl`es appears in selection box **1136**.

Returning to method **900** of FIG. 9, in operation **936**, a preferred execution order is determined for the links that were specified in operation **930**. Executing the links in the preferred order will reduce overall reformatting time relative to the time it would take to execute all such links in a random sequence. In one embodiment of a preferred execution order, links are sequenced such that:

(1) the destination well of each subsequent link is the closest well to the destination well of the previous link; and

(2) irrespective of item (1), links sourced from the same source well are executed before executing a link that draws from a different source well.

For example, assume the following group of links is specified:

Source Well (row, column)	Destination Well (row, column)
(2, 1)	(10, 15)
(2, 1)	(20, 30)
(2, 1)	(12, 25)
(7, 6)	(10, 16)

In accordance with the algorithm described above, these links would be sequenced from first to last as follows:

[(2,1) (10,15)] [(2,1) (12,25)] [(2,1) (20,30)] [(7,6) (10,16)].

It is within the capabilities of those skilled in the art to develop an algorithm that sequences links as described above. Moreover, it will be appreciated that other approaches for sequencing links that will likewise reduce overall execution time relative to a random execution sequence, as will occur to those skilled in the art in view of the present teachings, may suitably be used.

In the example described above, SCR control software **1046** operates such that even though more than one destination well may be receiving liquid from a single source well (assuming the transfer is to a denser format), the liquid transfer vehicle (*e.g.*, syringe **210**) returns to the source well for each transfer. In other words, even though a sufficient volume of liquid could be aspirated from the source well (*e.g.*, source well (2,1)) to supply a multiplicity of destination wells (*e.g.*, (10,15), (12,25), and (20,30)), a volume of liquid sufficient to supply only a single destination well is withdrawn, per aspiration, from the source well. In other embodiments, SCR control software **1046** is operative to withdraw a sufficient volume of liquid from a source well to supply multiple destination wells, as dictated by the specified links. Using such an approach in conjunction with item (1) of the sequencing algorithm further reduces reformatting time.

In operation **938**, the specified links are executed. Operation **938** can be initiated using GUI **1100** by "clicking" "start" icon **1140**. Start icon **1140** is advantageously grouped in control panel **1138** with a palette of other icons that are operable to initiate various functions. In the illustrated embodiment, control **1138** includes, in addition to start icon **1140**, "pause" icon **1142**, "e-stop" icon **1144**, "new" icon **1146**, "open" icon **1148**, "save" icon **1150** and "exit" icon **1152**.

Pause icon **1142** pauses the reformatting operation at any point. E-stop icon **1144** is an emergency stop that ends the reformatting run. New icon **1146** clears source and destination plate links and allows a user to specify new links. Open icon **1148** opens a saved file of links and save icon **1150** saves a series of links. Exit icon **1152** exits the software.

In one embodiment, "execution" operation **938** includes operations **940** through **944**. In operation **940**, spatial coordinates for source and destination wells of links are obtained. In some embodiments, such information is contained in updateable data file **1048** (*see* FIG. 10). In one embodiment, the information contained in updateable data file **1048** includes, for each plate format:

(1) the absolute position of one well (typically well 1,1) with the plate disposed in the source plate receiver **456** (*see* FIG. 3);

(2) the absolute position of one well (typically well 1,1) with the plate disposed in the destination plate receiver **462** (*see* FIG. 3); and

(3) the center-to-center well spacing for each format.

From this information, the spatial position of any well in a plate, with the plate in either the source position or the destination position, can be calculated in well known fashion. In another embodiment, the x-y-z coordinates of each well are stored in updateable data file **1048**.

In operation **942**, the spatial coordinates and other SCR control parameters (*e.g.*, syringe control parameters and wash system control parameters, *etc.*) are transferred to controller **1050**. Controller **1050** converts the spatial coordinates into actuator control information that drives, in operation **944**, x-y positioner **201**, z-positioner **206** and syringe drive **212** to aspirate liquid from the specified source wells and dispense the aspirated liquid into the specified destination wells. In terms of illustrative SCR **200** depicted in FIG. 3, the actuator control information is motor control information that drives, as appropriate, s-stepper motor **686**, z-stepper motor **570**, y-stepper motor **440** and x-stepper motor **1060** (not depicted in FIG. 3, *see* FIG. 10).

Those skilled in the art will recognize that a stepper motor driver operable to receive the motor control information from controller **1050** is required in conjunction with each stepper motor. The controller, which may be, for example, a 4-axis PC Card, is available from Acroloop Motion Control Systems of Chaska, Minnesota, and the stepper motor drivers are available from Applied Motion Products of Watsonville, California.

As will be appreciated by those skilled in the art, the various positioning systems described herein advantageously include a "home sensor" that provides a position reference to controller **1050**. As depicted in FIG. 10, information from x-home sensor **1070**, y-home sensor **1072**, z-home sensor **1074** and s-home sensor **1076** is transmitted, via controller **1050**, to processor **1042**. It is within the capabilities of those skilled in the art to suitably select a home sensor and integrate it for use with any of the positioners and/or drives mentioned herein. A suitable home sensor is available from Omron of Schaumberg, Illinois.

It will be appreciated that the functionality described above may be implemented in software in many different ways by those skilled in the art. For example, appreciable variation in the order in which various tasks/operations are accomplished can be expected, since the order of the operations comprising method **900** is substantially permutable. Moreover, a variety of different data structures can be developed for organizing the link data. An embodiment of one such data structure that provides certain efficiencies in terms of computer resources and processing time is described below in conjunction with FIG. 14.

To cover all possible links between wells on source plates and wells on destination plates would require an array having a maximum size of 1536 x 1536 (assuming a maximum plate density of 1536 wells). Thus, an array having 2.4 million data structures, each data structure containing the link data for a single link, would be required. The present inventors have substantially reduced the theoretical array size by recognizing that, notwithstanding the 2.4 million possible combinations, each well on the destination plate can link with only *one* well on the source plate. In other words, the link array can be reduced to a maximum of 1536 data structures, one data structure for each well on the destination plate. Such an array of data structures is depicted in FIG. 14.

Link array **1454** contains a number N of data structures $\mathbf{1456}_i$, where N is the number of wells in the destination plate. Each data structure $\mathbf{1456}_i$ contains row and column designation **1458** of a source well and row and column designation **1460** of a destination well. In some embodiments, each data structure $\mathbf{1456}_i$ includes link status **1462** for indicating whether the link is active (*i.e.*, liquid is being dispensed to that particular destination well) or not, and whether the link has been executed if it is active. Additionally, in some embodiments, each data structure $\mathbf{1456}_i$ contains an execution priority **1464** as determined in operation **936** of method **900** (*see* FIG. 9).

It is to be understood that the above-described embodiments are merely illustrative of the invention and that many variations can be devised by those skilled in the art without departing from the scope of the invention. It is therefore intended that such variations be included within the scope of the following claims and their equivalents.